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AUTHOR(S): Huan, Y.-H.; Van Adelsberg, J.
SOURCE: Journal of the American Society of Nephrology, (Sept., 1997) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 373A. Meeting Info.: 30th Annual Meeting of the American Society of Nephrology San Antonio, Texas, USA November 2-5, 1997 American Society of Nephrology . ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

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TITLE: Co- ***expression*** of the ***PKD*** - ***I*** protein with matrix receptor and adhesion plaque proteins in human fetal and ADPKD epithelia in vitro.
AUTHOR(S): Wilson, P. D. (1); Kaelin, W.; Burrow, C. R.
SOURCE: Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 245A. Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996 ISSN: 1059-1524.
DOCUMENT TYPE: Conference; Abstract; Conference
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Thanks a lot...

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TITLE: Co- ***expression*** of the ***PKD*** - ***1*** protein with matrix receptor and adhesion plaque proteins in human fetal and ADPKD epithelia in vitro.
AUTHOR(S): Wilson, P. D. (1); Kaelin, W.; Burrow, C. R.
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A1722

Phenotype PKD2 vs. PKD1: results from the European concerted action. H. Haebler, M. Dijk, R. Torra, N. Bogdanova, F. Davies, L. Lazarou, M. Brumming, A.K. Sagar-Malik, S. Jeffery, J.L. San Millan, I. Martinez, R. Walker, P. Holmans, D. Ravine and G.A. Coles. *Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK.*

Polycystic kidney disease type 2 (PKD2) has been consistently reported to have a milder clinical phenotype than PKD1. All reports to date have been limited to small numbers of families. Here we report the findings of a multicentre survey which aimed to define more precisely the clinical expression of PKD2. Clinical data from 306 PKD2 affected individuals within 32 Caucasian families were collected from 7 centres and then compared against data from 288 PKD1 affected individuals within 17 Caucasian families. Spouses and non-affected siblings served as controls. Survival analysis was used to compare age-at-event data in the populations, while differences in prevalence of complications between PKD1 and PKD2 individuals were assessed by logistic regression analysis to correct for age and sex. It was confirmed that PKD2 patients had a later onset of clinical presentation (median age 61.0 vs. 35 years) and longer overall survival than those with PKD1 (median age 69.8 vs. 53.6 years). Compared to controls, PKD2 patients died prematurely (median age 69.8 vs. 75.0 years). Renal survival in PKD2 was longer than in PKD1 (median age 74.0 vs. 60.3 years). PKD2 patients were less likely to be hypertensive (odds ratio 0.28, 95% CI 0.16-0.48), less likely to have a history of renal infection (0.47, 0.28-0.81), less likely to suffer a subarachnoid haemorrhage (0.18, 0.07-0.47) and less likely to develop a hernia (0.46, 0.22-0.98). In contrast to previous reports no parent of origin or gender effects were observed in either PKD1 or PKD2.

Conclusion: PKD2 patients have a reduced life expectancy compared to normal controls, but, compared with those with PKD1, have a milder clinical course with longer survival and fewer clinically significant complications.

A1723

Autosomal dominant polycystic kidney disease (ADPKD) in African Americans: Prevalence and clinical course. J.K. Heifner and L.M. Guay-Woodford. *Dept. of Med. and Dept. of Pediatr., UAB, Birmingham, AL, USA.*

ADPKD is the most common hereditary renal disease in the US, accounting for 8% of ESRD in Caucasians (C). Comparatively little is known about the prevalence and renal progression factors associated with ADPKD in African Americans (AA). We sought to determine the prevalence, clinical course and genetic factors (frequency of PKD1 vs PKD2 and sickle cell trait) associated with ADPKD in this racial group.

Among ESRD patients in Alabama, 44 (1.7%) AA vs 96 (7.5%) C had ADPKD in 1995 (Network 8 data). However, after adjusting for population rates, the prevalence of ESRD is similar in these two groups (4.31/100,000 in AA vs. 3.22/100,000 in C). We have reviewed the UAB Hospital databases and identified 38 AA with ADPKD. Of these, 25 (66%) had developed ESRD (mean: 50.4 yrs) and no gender difference was apparent (males: 50.7 yrs; females: 50.1 yrs). These data are consistent with those previously reported in AA (Yium IASN, 1994) but the younger mean age and the absence of gender effect differ significantly from C data (Parfrey NEJM, 1990). These AA ESRD patients also differed from reported C cohorts in the incidence of hypertension (HTN) (76% AA vs 88% C) and frequency of > 2 episodes of gross hematuria (62% AA vs 42% C). In addition, 8/8 AA patients had urinary protein excretion > 300 mg/day prior to developing ESRD. In comparison, the 13 AA ADPKD patients without ESRD were younger (mean age 36.6 yrs vs 54.5 yrs), had less frequent HTN (61.5%); had fewer episodes of gross hematuria (38.5%), or significant proteinuria > 300 mg/d (28.6%).

We Conclude: a) the prevalence of ADPKD-related ESRD is not significantly different in AA patients vs. C; b) unlike C, AA have an earlier age of onset of ESRD; and c) factors affecting renal progression (gender, HTN and episodes of gross hematuria) differ between AA and C ADPKD patients. We speculate that other race-specific factors may influence disease progression in AA ADPKD patients.

A1724

Characterization of the paracrine renal endothelin system in polycystic kidneys of Han: SPRD rats. B. Hoche^{1,2}, R. Zart^{1,2}, N. Braun³, C. Thöne-Reineke², A. Schwarz^{1,2}, C. Bauer², H.H. Neumayer¹ and P. Rohmeiss². *Department of Nephrology, Charité, Humboldt University of Berlin; ¹Inst. of Molecular Biology and Biochemistry, Free University of Berlin; ²Department of Nephrology, Klinikum Mannheim, University of Heidelberg, Germany.*

Polycystic kidney disease (PKD) is characterized by structural alterations such as thickening of the tubular basement membrane, interstitial fibrosis and formation of cysts. Interestingly, interstitial fibrosis, glomerulosclerosis and cyst formation was also seen in human endothelin-1 transgenic mice. We therefore analyzed the tissue concentrations of ET-1 as well as the expression of endothelin receptor subtypes in the kidneys of young homozygously (cy/cy, 6-weeks-old), young and old heterozygously (cy/+, 6-weeks-old, 6-

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month-old) affected male Han:SPRD rats in comparison to age-matched controls. Furthermore, we investigated the acute effects of the mixed (A/B) endothelin receptor antagonist bosentan on haemodynamic and renal function in 6-month-old conscious chronically instrumented (cy/+) rats compared with age-matched littermates. The kidneys of affected rats showed significantly elevated tissue levels of ET-1 compared to age-matched controls (3.5 ± 0.3 -fold in young cy/cy rats, $p < 0.01$; 1.4 ± 0.2 -fold in young cy/+ rats, $p < 0.01$; 6.2 ± 0.4 -fold in old cy/+ rats, $p < 0.001$) due to a highly increased ET-1 synthesis within the epithelial cells of the cysts as shown by immunohistochemistry. Scatchard analysis - on the other hand - revealed a markedly decreased ETA as well as ETB receptor density (B_{max}) in all groups of affected rats (decrease in B_{max} compared to age-matched controls; ETA: 3.6 ± 0.7 -fold in young cy/cy rats; $p < 0.001$, 2.5 ± 0.4 -fold in young cy/+ rats, $p < 0.05$; 2.9 ± 0.2 -fold in young cy/+ rats, $p < 0.01$; ETB: 6.8 ± 0.7 -fold in young cy/cy rats, $p < 0.001$; 4.7 ± 0.5 -fold in young cy/+ rats, $p < 0.001$ and 2.2 ± 0.3 -fold in old cy/+ rats, $p < 0.01$). The acute blockade of both endothelin receptor subtypes using bosentan in 6-month-old heterozygous PKD rats led to a significant decrease in mean arterial blood pressure (MAP) (-19.7 ± 2.1 mmHg, $p < 0.05$) and a significant increase in renal blood flow (RBF) ($+2.1 \pm 0.5$ ml/min, $p < 0.05$), while bosentan had no effect on MAP and RBF of age-matched controls.

Conclusions: These data shows that the renal paracrine ET system is activated in PKD and might contribute to renal cyst formation and renal fibrosis. Furthermore, the ET system seems to be involved in the regulation of blood pressure and renal blood flow in PKD.

A1725

Peptides derived from the PKD1 repeats of polycystin inhibit kidney development *in vitro* by an effect on the ureteric bud. Y.-H. Huan and L. van Adelsberg. *Columbia University, New York, NY, USA.*

The function of polycystin, the product of the PKD1 gene, is not known. Its primary structure suggested that it might be a receptor. Peptides derived from the ligand binding domains of cell adhesion molecules like VCAM, NCAM and other immunoglobulin (Ig) repeat proteins block the interactions of these receptors with their ligands. The PKD1 repeats of polycystin are predicted to be similar to the immunoglobulin domains of these proteins. In Ig repeats, the ligand binding domain follows a conserved tryptophan (W) in the third β strand of the repeat. In PKD1 repeats, the structurally analogous ligand binding domain contains a peptide sequence WDFGDGS conserved in the majority of PKD1 repeats in both human and murine polycystin (C. Löhning, ICRF). Peptides containing the WDFGDGS sequence were therefore tested as competitive inhibitors of polycystin.

We showed that polycystin is expressed in a temporally and spatially regulated manner during renal development, suggesting that polycystin might play a role in renal morphogenesis. We reasoned that WDFGDGS peptides might have a measurable effect on renal development. To quantitate the effects of peptides on renal development, we isolated murine kidney rudiments at embryonic day 12.5, when the ureteric bud had branched a single time. Rudiments were grown in WDFGDGS peptides or scrambled control peptides for 5 days. The effect of peptides was quantitated by counting the number of glomeruli in whole mounts of kidney rudiments stained with peanut lectin and analyzed by confocal microscopy.

We found that WDFGDGS peptides reduced the number of glomeruli vs. control peptide treated kidneys by approximately 60% in seven independent experiments. The K_i for this effect was between 0.01 and 0.1 mM. Longer peptides were more effective inhibitors. A disulfide-bonded multimeric protein was isolated from fetal kidney extracts by peptide affinity chromatography. This protein was eluted by WDFGDGS but not scrambled peptides. We propose that this molecule is a candidate polycystin ligand.

We analyzed the effects of WDFGDGS peptides on kidney development and found that the peptide treated kidneys had developed outgrowths of the ureteric bud resulting in focal dilations of the ductular part of the ureteric bud and in non-dichotomous branching. These results suggest that inhibition of polycystin-ligand interactions induces *de novo* proliferation in the ductular part of the ureteric bud.

M751 (PS)

Characterization of the paracrine renal endothelin system in polycystic kidneys of Han: SPRD rats. B. Hoche^{1,2}, R. Zart^{1,2}, N. Braun³, C. Thöne-Reineke², A. Schwarz^{1,2}, C. Bauer², H.H. Neumayer¹ and P. Rohmeiss². *Department of Nephrology, Charité, Humboldt University of Berlin; ¹Inst. of Molecular Biology and Biochemistry, Free University of Berlin; ²Department of Nephrology, Klinikum Mannheim, University of Heidelberg, Germany.*

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